Pediatric Dimensions

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Anemia in new born

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Introduction

Anemia in the new born is the commonest hematological problem. Immediately following birth, all infants universally experience a decrease in hemoglobin (Hb) that results in varying degrees of anemia. The ultimate severity and rapidity with which this anemia develops are determined by a combination of multiple physiologic and non-physiologic processes. Preterm infants are especially vulnerable to these processes for two reasons. Firstly, the severity of the developmental postnatal decrease in Hb is most pronounced in the least mature infants, placing them at higher risk of developing clinically significant anemia. Secondly, as a group, preterm infants are particularly prone to developing electrolyte and acid-base imbalance, and infective illnesses, the diagnosis and management of which requires frequent laboratory assessment, resulting in significant phlebotomy loss. It is the combination of developmentally regulated physiologic processes (anemia of prematurity [AOP]) along with concomitant pathologic and iatrogenic processes that contribute to the progressive anemia experienced by virtually all preterm infants.

The causes of anemia in newborns can be prenatal, natal or postnatal. Usually the diagnosis will be straight forward if approached in a systematic manner. The objective of this review is to discuss the physiology, the causes, clinical presentation and approach to the newborn anemia.

Physiology

The process of haematopoiesis begins as early as 3rd week of gestation in the yolk sac [1]. From 11-12 weeks of gestation, liver is the organ of haematopoiesis [2]. Bone marrow erythropoiesis switch happens around 30 weeks of intrauterine life & at birth, marrow erythropoiesis is major site for blood cells production [3].

In utero, the oxygen saturation in aortic blood is around 45%, erythropoietin levels are high, and red blood cells production is rapid. Soon after birth, the oxygen saturation goes up to 95%, down regulating the erythropoietin mediated red cell production. The erythropoietin will become undetectable by 3 days after birth with reduction in reticulocyte counts and thus haemoglobin levels [4].

At birth the haemoglobin levels is 14.9 g/dl-23.7 g/dl in term and 19.1 g/dl-22.1 g/dl in preterm babies. It rapidly falls to 9.5-11 g/dl by 9-11 weeks of postnatal period in term babies and 6.5-9 g/dl by 4-8 weeks in preterm babies [5]. After reaching this nadir, the infant's marrow starts its erythropoiesis. The iron released from breakdown of these RBCs is stored in the liver, which in turn is utilised for erythropoiesis. Usually term babies have sufficient iron stores till 5 months of age for active erythropoiesis, after which iron needs to be supplemented by iron rich complementary foods. Preterm babies require iron supplementation from as early as 2-3 weeks of post natal age continued through their first year of life. Simultaneously there is increase in 2,3- diphosphoglycerate in red blood cells as slowly adult haemoglobin (HbA) replaces fetal haemoglobin (HbF) during the first half of infancy [6-8]. HbA has very less affinity for oxygen as compared to HbF, thus even with falling hemoglobin levels, the oxygen delivery to the tissues actually increases.

Preterm babies have added problems like, poor general condition, reduced life span of RBC (35-40 days *vs.* 60-70 days of term babies) [9], increased phlebotomy losses, accelerated growth rate, poor iron stores and inappropriate bone marrow response making them at the risk of exposure to repeated transfusions. In general, even term neonates with normal haemoglobin at birth would have depleted their iron stores by the time they have doubled their birth weight [10].

The influence of cord clamping

The other major influence on haemoglobin concentration at birth is the timing of cord clamping and the position of the baby at the time of clamping. In term babies, the placental vessels contain around 100 ml of blood at birth. It has been estimated that 25% of the placental blood is transfused within the first 15 seconds and 50% (*i.e.,* 50 ml in a term baby) by the end of the first minute [11]. The difference in hemoglobin concentration in the baby between early and late cord clamping is around 3 g/dl [12]. Babies held below the level of the placenta continue to gain blood until the cord is clamped and have higher haemoglobin levels than those held above the level of the placenta, who may lose blood into the placenta until the cord is clamped [13].

Causes

1. Impaired red cell production

Diamond–Blackfan anaemia

Congenital infection, e.g. cytomegalovirus, rubella

Congenital dyserythropoietic anaemia

Osteopetrosis

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Pearson syndrome

Congenital leukaemia

Drug induced suppression

2. Increased red cell destruction (haemolysis)

Alloimmune: haemolytic disease of the newborn (Rh, ABO, Kell, others)

Autoimmune, e.g. maternal autoimmune haemolysis

Red cell membrane disorders, e.g. hereditary spherocytosis

Red cell enzyme deficiencies, e.g. pyruvate kinase deficiency, G6PD deficiency

Some hemoglobinopathies, e.g. α-thalassemia major, HbH disease

Infection, e.g. bacterial, syphilis, malaria, cytomegalovirus,

Toxoplasma, herpes simplex

Macro/microangiopathy, e.g. cavernous haemangioma, disseminated intravascular coagulation

Galactosaemia, vitamin E deficiency

3. Blood loss

Occult haemorrhage before or around birth, e.g. twin-to-twin, fetomaternal, ruptured vasa praevia, abruption placenta, placenta previa, cord rupture

Internal haemorrhage, e.g. intracranial, subaponeurotic, Intraperitoneal, ruptured liver/ spleen, adrenal hemorrhage, NEC

Iatrogenic: due to frequent blood sampling

4. Anaemia of prematurity

Impaired red cell production plus reduced red cell lifespan

Table 1. Differential diagnosis and management of anemia in the newborn.

Age	Hemoglobin (g/dl)	Hematocrit (%)	Mcv (µ3)	Reticulocytes (%)
Gestational (wk)				
18-20*	11.5 +/- 0.8	36 +/-3	134 +/-8.8	N/a
21-22*	12.3 +/- 0.9	39 +/- 3	130 +/-6.2	N/a
23-25*	12.4 +/- 0.8	39 +/-2	126 +/-6.2	N/a
26-27	19.0 +/-2.5	62 +/-8	132 +/-14.4	9.6 +/-3.2
28-29	19.3 +/-1.8	60 +/-7	131 +/-13.5	7.5 +/-2.5
30-31	19.1 +/-2.2	60 +/-8	127 +/-12.7	5.8 +/- 2.0
32-33	18.5 +/-2.0	60 +/-8	123 +/-15.7	5.0 +/-1.9
34-35	19.6 +/-2.1	61 +/-7	122 +/-10.0	3.9 +/-1.6
36-37	19.2 +/-1.7	64 +/-7	121 +/-12.5	4.2 +/-1.8
38-40	19.3 +/-2.2	61 +/-7	119 +/-9.4	3.2 +/-1.4
Postnatal (days)				
1	19.0 +/-2.2	61 +/-7	119 +/-9.4	3.2 +/-1.4
2	19.0 +/-1.9	60 +/-6	115 +/-7.0	3.2 +/-1.3
3	18.7 +/-3.4	62 +/-9	116 +/-5.3	2.8 +/-1.7
4	18.6 +/-2.1	57 +/-8	114 +/-7.5	1.8 +/-1.1
5	17.6 +/-1.1	57 +/-7	114 +/-8.9	1.2 +/-0.2
6	17.4 +/-2.2	54 +/-7	113 +/-10.0	0.6 +/-0.2
7	17.9 +/-2.5	56 +/-9	118 +/-11.2	0.5 +/-0.4
Postnatal (wk)				
1-2	17.3 +/-2.3	54 +/-8	112 +/-19.0	0.5 +/-0.3
2-3	15.6 +/-2.6	46 +/-7	111 +/-8.2	0.8 +/-0.6
3-4	14.2 +/-2.1	43 +/-6	105 +/-7.5	0.6 +/-0.3
4-5	12.7 +/-1.6	36 +/-5	101 +/-8.1	0.9 +/-0.8
5-6	11.9 +/-1.5	36 +/-6	102 +/-10.2	1.0 +/-0.7
6-7	12.0 +/-1.5	36 +/-5	105 +/-12.0	1.2 +/-0.7
7-8	11.1 +/-1.1	33 +/-4	100 +/-13.0	1.5 +/-0.7
8-9	10.7 +/-0.9	31 +/-3	93 +/-12.0	1.8 +/-1.0
9-10	11.2 +/-0.9	32 +/-3	91 +/-9.3	1.2 +/-0.6
10-11	11.4 +/-0.9	34 +/-2	91 +/-7.7	1.2 +/-0.7
11-12	11.3 +/-0.9	33 +/-3	88 +/-7.9	0.7 +/-0.3
12-14	11.9	37	86.8	0.9

Clinical manifestations

A detailed antenatal history including records of antenatal sonological reports gives a lot of information. Twin-twin transfusion can very well be diagnosed antenatally. Obtaining a peak systolic velocity of middle cerebral artery gives an indirect estimation of anemia as well as a guide to antenatal therapy [13]. Details of labour, presentation, instrumental delivery, birth injury, cord accidents and other details should be collected.

Family history of anemia, cholelithiasis, splenectomy, unexplained jaundice may point towards a possible haemolytic anemia. Any medication given to the baby must be checked.

Presentation can vary from being asymptomatic to hydrops and congestive cardiac failure. Chronic anemia can present as pallor without much distress whereas acute blood loss presents in shock in presence of normal Hb values. Unexplained tachycardia, oxygen requirement, prolonged unconjugated jaundice, not gaining adequate weight are very non-specific symptoms. Presence of hepatospleenomegaly may point for haemolytic jaundice or congenital infections. Congenital infections in addition can have chorioretinitis, pneumonitis, osteoarthritis, IUGR etc. Congenital anemia syndromes will have skeletal abnormalities.

Evaluation

1. Complete hemogram including, haemoglobin levels, retic count, peripheral smear study, red blood cell count, RBC indices should be evaluated. The values must be interpreted in the background of normal range (Table 1 and 2) (capillary sample Hct is 2.7%-3.9% higher than venous) [14]. Hb value of less than 14 gms% in the first week of life is considered anemia in newborn period [15].

2. MCV values will be more in newborn period (105-125fl *vs.* 75-90fl in children). A value of less than 95fl is considered as microcytic. MCH is also more till 8-10 weeks of postnatal age (35-38 pg *vs.* 30-33 pg). hypochromia is when MCH is less than 34 pg [16]. Microcytic and hypochromic is commonly seen with chronic hemolysis, blood loss or thalassemia disorders (└ and γ thalassemia).

3. Reticulocyte counts in children and adult are 1%-2%. In term babies the reticulocyte counts are 3%-7% which falls to 1% by the end of first week of life. Preterm babies will have slightly more number (6%-10%) as also persists till 2-3 weeks of life [17].

4. Nucleated RBCs are also markers of hemolysis in the absence of asphyxia. They are normally not detectable in the peripheral circulation beyond first week of life in term babies, though in preterm babies they can persist up to 4 weeks.

5. Peripheral smear examination- look for the evidence of hemolysis, spherocytosis, elliptocytes other size and shape of red blood cells. Decreased cells indicate a hypo plastic/aplastic condition which may be a primary or secondary aplastic anemia. Presence of abnormal cells may indicate congenital leukaemias.

Table 2. Effects of early erythropoietin therapy.

Hematocrit (%)	Hemoglobin (g/dl)	Respiratory support and/or symptoms	Transfusion volume
≤35	≤11	Infants requiring moderate or significant mechanical ventilation (mean arterial pressure >8 cm h_2o and fio_2>0.4)	15 ml/kg prbcs* over 2-4 hr
≤30	≤10	Infants requiring minimal respiratory support (any mechanical ventilation or endotracheal/nasal continuous positive airway pressure >6 cm h_2o and fio_2 ≤0.4)	15 ml/kg prbcs over 2-4 hr
≤25	≤8	Infants not requiring mechanical ventilation but who are receiving supplemental o2 or cpap with an fio2 ≤0.4 and in whom 1 or more of the following is present: • ≤24 hr of tachycardia (heart rate >180 beats/min) or tachypnea (respiratory rate >80 breaths/min) • An increased oxygen requirement from the previous 48 hr, defined as a ≥4-fold increase in nasal canula flow (i.e., from 0.25 to 1 l/min) or an increase in nasal cpap ≥20% from the previous 48 hr (i.e., 5 to 6 cm h2o) • Weight gain <10 g/kg/day over the previous 4 days while infant is receiving ≥100 kcal/kg/day • An increase in episodes of apnea and bradycardia (>9 episodes in a 24-hr period or ≥2 episodes in 24 hr requiring bag and mask ventilation) while infant is receiving therapeutic doses of methylxanthines • Undergoing surgery	20 ml/kg prbcs over 2-4 hr (divide into 2 10-ml/kg volumes if infant is fluid sensitive)
≤20	≤7	Asymptomatic and an absolute reticulocyte count <100,000 cells/l	20 ml/kg prbcs over 2-4 hr (2 10-ml/kg volumes)

6. Direct antiglobulin test (DAT)/ direct coomb's test (DCT) - detects the presence of antibody coated red blood cells. It is positive in cases of isoimmunisation due to Rh incompatibility and in less proportion of isoimmunisation due to ABO, Kell or other minor blood group incompatibilities.

7. Enzyme assay for G6PD deficiency, pyruvate kinase deficiencies.

8. Haemoglobin electrophoresis requires expertise for interpretation as the predominant fetal haemoglobin(HbF) will get replaced by adult haemoglobin (HbA) during the early neonatal period.

9. Kleihauer-Betke test or by flow cytometry methods - fetal cells in maternal blood can be detected in cases of feto-maternal transfusions.

10. Congenital parvo viral infection can be diagnosed by PCR method.

11. Imaging studies for occult bleeding into organs should be considered when history and clinical examinations are suggestive of the same.

12. Congenital syndromes like Diamond Blackfan anemia, Pearson syndrome, congenital dyserythropoietic anemia, may require bone marrow examination and other specific tests.

Management

The widely practiced treatment option for anemia in infants is packed red cells transfusion. There are guidelines for transfusions in neonates. Many trials have compared the benefits and adverse outcomes of 'restricted' versus 'liberal' approach for transfusion.

Red blood cells transfusion

Packed red blood cells are the product of choice for transfusion when indicated. 10-15 ml/kg of PRBC transfusion is recommended over a period of 3-4 hours. Each 3 ml/kg of transfused PRBC raises Hb levels by 1 gm%. In cases of hemorrhagic shock whole blood transfusions can be considered if available. In a small study of 30 transfusions in 13 infants (birth weight 500–1500 g), comparing 10 *vs.* 20 ml/kg, it was found that the use of a larger volume (20 ml/kg) results in a higher post-transfusion Hb without negative respiratory effects [18]. Blood currently available in most of the blood bank is Citrate-Phosphate-Dextrose (CPD), or CPD-adenine (CPDA-1) or adenine-saline (AS-3) with a half-life of 21, 35 & 42 days respectively. Older blood has more potassium along with reduced 2, 3 - DPG levels. Fresh blood within 4-5 days is desirable. Designation of a single AS-3 preserved red cell donation for use by one neonate is an effective way to limit the donor exposure and transfusion associated risks [19].

Leukocyte filtration- all the donors must be screened and ensured that they are CMV infection free. Preterm babies are at a higher risk of acquiring transfusion related infection particularly CMV as they lack immunity. The effective way to reduce the risk of CMV transmission is by using leukocyte filters [20].

Irradiation- the risk of graft versus host disease (GVHD) is highest in preterm babies. It should be ensured that all the transfusions to preterm babies must be irradiated. The half-life of RBC which is irradiated gets reduced by 4-5 days and there may be risk of hyperkalemia. Currently there is no recommendation to use the irradiated PRBC in term baby transfusions [21,22].

In addition, several recentstudies found an increased risk for necrotizing enterocolitis (NEC) in neonates after RBC transfusions, so-called 'transfusion-associated NEC.' Whether transfusion-associated NEC reflects a causal relation between blood transfusions and the development of NEC or only an indirect association is still controversial. Transfusion-related lung injury, acute respiratory distress with lung infiltrations, is a well-known complication in adult transfusion medicine. It has also been recognized in children but has hardly been described in neonates.

A recent Cochrane review evaluated the results of four randomized controlled trials with a total of 614 infants, comparing lower (restrictive) versus higher (liberal) transfusion thresholds in preterm infants. In this meta-analysis, no significant differences were found in mortality or severe neonatal morbidity, or in long-term neurodevelopmental outcome between the two groups.

Erythropoietin- (rHuEPO)

Many studies have shown that preterms treated with rHuEPO will have less number of transfusions and hence less risk of transfusion associated problems. There are studies comparing early (<7 days) versus late rEPO treatment. rHuEPO doesn't reduce the number of transfusions required by preterm babies in early neonatal life where as the late requirement of transfusions can be reduced significantly. Moreover the dose required may be higher upto 250-300 IU/kg, thrice a week; it also requires iron supplementation of 2-3 mg/kg/day. There is also concern over the increased incidence of ROP in premature babies treated with rHuEPO in early life.

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Conflict of Interest

The authors have no potential conflicts of interest to disclose.

Clinical Trial Registration

Not applicable.

Contributors' Statements

Dr R. Kishore Kumar: conceptualized and designed the study, critically analysed the manuscript, and approved the final manuscript as submitted. Dr Nandini Nagar: Dr. Nandini wrote the initial draft, reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr Prashanth Sarnadgoud was involved in collecting data, drafting the initial manuscript and approving the final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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